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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,944	HERRMANN, JOHN ET AL	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,9,12-14,19-21,39 and 42* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,9,12-14,39 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Hermann *et al*
Priority Date: 4 October 2000

Election/Restrictions

1. Applicant's election with traverse of group II (claims 5-14,39, and 42)in the reply filed on 8/3/2004 is acknowledged. The traversal is on the ground(s) that the invention of group II and V can be examined together because the search for the different groups would not be burdensome and would be overlapping. More specifically, applicant argues that a search for the detection steps of group V would also encompass a search of the invention of group II. This is not found persuasive because the search for the different groups would impose a search burden. Specifically, the inventions are distinct because they have acquired separate status in the art as shown by their different classifications. Moreover, in the instant case, the search for the polynucleotides and the method of determining the presence of the nucleic acid in the sample are not coextensive. Group II encompasses molecules, which are claimed by reference to nucleic acid and protein sequences of SEQ ID NO: 1 and 2. In contrast, the search for group V would require a text search for the method of determining the presence of the nucleic acid of group II. If the prior art teaches a polynucleotide identical to SEQ ID No: 1, it would not necessarily be applicable to the method of group V. Moreover, even if the polynucleotide product were known, the method of determining the presence of the polynucleotide of group II may be novel and unobvious in view of the preamble or active steps. And finally, because the applicant elected the invention of group II instead of the

invention of group V, it would not necessarily require a search for the "detection steps" as argued because the search for the nucleic acid sequence does not need to be performed in the context of detecting.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-4, 7-8,10-11,15-18,22-38, and 40-41 are canceled without prejudice.

3. Claims 5-6,9,12-14,19-21,39, and 42 are pending, claims 19-21 are withdrawn from further consideration as being drawn to a non-elected invention.

4. Claims 4-6,9,12-14, 39, and 42 are examined on the merits.

Information Disclosure Statement

5. The Information Disclosure Statements filed 11/18/2002 and 8/5/2004 are acknowledged and considered. A signed copy of the IDS is attached hereto.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see for example, the specification on page 170). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has set forth an isolated nucleic acid sequence represented by SEQ ID No: 1. Because SEQ ID No: 1 represents the sense strand, one of skill in the art would be able to recognize the full complement of SEQ ID No: 1 or anti-sense strand and therefore the written description in this case is not commensurate in scope to the claim that reads on any sequence that is complementary to that of SEQ ID No: 1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular

chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant genes encoding the proteins of SEQ ID No: 2 defined. With the exception of SEQ ID No: 1, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and or complements and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula,

chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants and complements is provided in the specification on page 16 lines 4-19 where it is disclosed that nucleic acids encoding the UNC5-like proteins include "mutants or variants of the nucleic acid any of whose bases may be changed from the corresponding base", which also include those "nucleic acid whose sequences include complementary" sequences. Because the term "complementary" has been defined, as including the traditional Watson-Crick base pair scheme (see page 63) and because the specificity of hybridization has not been defined, the term encompasses any sequence that is able to hybridize to SEQ ID No: 1 under any conditions, and as such represents a broad genus of sequences, none of which have been defined or disclosed in the specification. No disclosure, beyond the mere mention of allelic variants or complements is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only the nucleic acid of SEQ ID No: 1 encoding the protein of SEQ ID No: 2. and the full complement of SEQ ID No: 1 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 101 &

35 USC § 112, 1st paragraph

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 5-6,9,12-14,39, and 42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The disclosed utilities for the NOV 1 nucleic acid (SEQ ID No: 1), which encodes the NOV 1 protein (SEQ ID No:2) include the administration of the nucleic acid as a therapeutic such as in gene therapy (see page 4, lines 1-9 and page 5 lines 4-6) and methods of determining the presence of a disease using the NOVX nucleic acids (see page 4, lines 27-34). More specifically, it is disclosed that the NOV1 nucleic acid shares a high degree of homology to the UNC5-like family of proteins and that NOV 1 can be used to treat metastatic potential and invasion (see page 6, lines 12-15). However, neither the specification nor any art of record teaches what NOV 1 is, how it functions, or a specific and well-established utility for the nucleic acid or for the protein it encodes. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. What the specification does disclose however, is the relative nucleic acid expression levels of the NOV1 nucleic acid in tissue samples (see pages 138-142). The specification also asserts that the utility of the NOV 1 nucleic acid would thus encode a NOV 1 protein that has properties similar to other proteins having similar domain structures (see page 13, lines

30-32). As a result, the specification indicates that the invention would thus encode a UNC5-like protein which would "function as a member of the UNC5 family" and then concludes that the instant invention would encode a protein useful as a therapeutic modality for diseases involves with NOV 1 proteins (see pages 16-17). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and

biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard

to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the function of the NOV 1 protein (SEQ ID NO:2) encoded by SEQ ID No: 1 can not be predicted, based on sequence similarity with other proteins comprising similar domain structures.

According to the Federal Guidelines (Fed. Reg. Vol. 66, No. 4, January 5, 2001), an isolated and purified nucleic acid molecule may meet the statutory utility requirement if,

e.g., it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene. However, based on the disclosure it cannot be predicted that the isolated nucleic acid actually encodes a functional protein, nor does the specification or any art of record teach a relationship to any specific disease or establish any involvement of the invention in the etiology of any specific disease.

These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, despite the sequence or presence of domain structures that are present in other proteins with know functions, this type of analysis alone cannot predicted the function or properties of the instant protein, namely NOV 1. Further even if the polypeptide of SEQ ID NO:2, which is encoded by the nucleic acid of SEQ ID No: 1 is structurally similar to other proteins with known properties, neither the specification nor any art of record teaches what the polypeptide is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active as claimed in a pharmaceutical composition. Relative expression of the nucleic acid in tissues alone does not correlate to involvement in disease, because it is well known and taught in the art that nucleic acid expression levels do not always correlate to expression of the protein itself.

It is well established in the art that the control of protein translation is a highly regulated event (Jansen, M et al, 1995, Pediatric Res, 37 (6): 681-686). Those of skill in the art also recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example,

Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be over expressed in CHO cells following exposure to radiation, without any concomitant over expression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and

translation. For the above reasons, one of skill in the art would not be able to predict if over expression of the nucleic acid of SEQ ID No: 1 is indicative of the over expression of the protein represented by SEQ ID NO: 2. And finally, the specification has not established how these relative expression levels would be useful for any applicable use in the prediction or assessment of a disease.

Thus, the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide and fragments thereof. Because the claimed invention is not supported by a specific and substantial utility for the reasons set forth, credibility of any utility cannot be assessed.

Claims 5-6,9,12-14,39, and 42 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
October 13, 2004

GARY NICKOL
PRIMARY EXAMINER